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Intensive exercise training suppresses testosterone during bed rest

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Wade, C. E., K. I. Stanford, T. P. Stein, and J. E. Greenleaf. Intensive exercise training suppresses testosterone during bed rest. *J Appl Physiol* 99: 59–63, 2005. First published February 10, 2005; doi:10.1152/japplphysiol.00332.2004.—Spaceflight and prolonged bed rest (BR) alter plasma hormone levels inconsistently. This may be due, in part, to prescription of heavy exercise as a countermeasure for ameliorating the adverse effects of disuse. The initial project was to assess exercise programs to maintain aerobic performance and leg strength during BR. The present study evaluates the effect of BR and the performance of the prescribed exercise countermeasures on plasma steroid levels. In a 30-day BR study of male subjects, the efficacy of isotonic (ITE, $n = 7$) or isokinetic exercise (IKE, $n = 7$) training was evaluated in contrast to no exercise ($n = 5$). These exercise countermeasures protected aerobic performance and leg strength successfully. BR alone (no-exercise group) did not change steroidogenesis, as assessed by the plasma concentrations of cortisol, progesterone, aldosterone, and free (FT) and total testosterone (TT). In the exercise groups, both FT and TT were decreased ($P < 0.05$): FT during IKE from 24 ± 1.7 to 18 ± 2.0 pg/ml and during ITE from 21 ± 1.5 to 18 ± 1 pg/ml, and TT during IKE from 748 ± 68 to 534 ± 46 ng/dl and during ITE from 565 ± 36 to 496 ± 38 ng/dl. The effect of intensive exercise countermeasures on plasma testosterone was not associated with indexes of overtraining. The reduction in plasma testosterone associated with both the IKE and ITE countermeasures during BR supports our hypothesis that intensive exercise countermeasures may, in part, contribute to changes in plasma steroid concentrations during spaceflight.

countermeasures; steroidogenesis; cortisol; progesterone; catecholamines

COUNTERMEASURES ARE BEING developed to alleviate some of the adverse effects of spaceflight (10–13). The end point for efficacy of a countermeasure is usually the prevention of a specific symptom, with little regard for confounding factors. Heavy exercise has been advocated as an effective countermeasure to attenuate loss of bone and muscle mass during spaceflight, as well as to reduce the incidence of orthostatic intolerance on return to Earth (10–13, 33). The secondary effects of heavy daily exercise, specifically overtraining, have not been investigated (33). One of the primary effects of overtraining on Earth is reduction of testosterone in men and decrease in estrogen in women (3, 6, 8, 16, 17, 24, 34). The reduction in reproductive steroids, as well as changes in progesterone and aldosterone levels, may be the result of a shift in steroid synthesis favoring production of cortisol in response to a stressful situation. Testosterone and estrogen are important in the maintenance of normal reproductive, bone, and muscle health. They also play a role in cardiovascular function and modulate responses of the immune and endocrine systems to stress. Thus, if prescription of heavy exercise daily as a countermeasure leads to overtraining, there may be negation of its beneficial effects due to reduced testosterone levels.

Responses of steroids during spaceflight have been inconsistent (14, 32); cortisol levels during spaceflight are increased or unchanged (15, 25, 26, 29, 30, 32); concentrations of aldosterone are increased, unchanged, or reduced (14, 15, 23); and testosterone is reduced or unchanged (29–32). Similar inconsistencies have been noted during bed rest (BR) used to simulate the effects of spaceflight. During BR, plasma cortisol levels have been reported to be increased (35) or unchanged (2), whereas aldosterone was reduced (35) or increased (18–21). Alterations in steroid levels appear to be highly dependent on the nature of the spaceflight mission due to uncontrolled factors, such as reduced caloric consumption, high-energy expenditure requirements, and various countermeasures, including heavy exercise, that contribute to negative energy balance (26–28, 38).

One specific problem of a heavy-exercise training regimen is induction of the overtraining syndrome (OTS) in which the body does not recover readily (8, 34). Symptoms of OTS are as follows: a sudden drop in physical and psychological performance, an increase in resting heart rate, an increase in serum enzymes related to possible muscle damage, and an alteration of the levels of numerous hormones, including the steroids (4–6, 8, 34, 36, 37).

We hypothesized that the variability in hormone levels, specifically the reduction in plasma testosterone concentrations (29–32) during spaceflight, might be related to the use of intensive exercise training, resulting in OTS. To evaluate this hypothesis, data from a 30-day BR study, as a surrogate of spaceflight, were analyzed to investigate the effects of short-term, high-intensity isotonic and isokinetic exercise training to establish whether various hormonal changes were the result of BR, exercise, or OTS.

METHODS

Nineteen men (aged 32–42 yr), who passed a comprehensive medical examination and participated in an extensive briefing and discussion, gave their informed, written consent to the experimental conditions, in accordance with the National Aeronautics and Space Administration human use protocol that was approved by the Institutional Review Board. All subjects were nonsmokers, and none took nonprescribed medications. They were of average anthropometric composition and working capacity: age, 36 ± 1 yr; height, 178 ± 2 cm; weight 76.5 ± 1.8 kg; peak O_2 uptake ($\dot{V}O_2$; supine), 3.36 ± 0.12 l/min (44 ± 2 $ml \cdot min^{-1} \cdot kg^{-1}$); leg strength [(flexion + extension)/

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2], 690 ± 23 N·m (10–13). No adverse health problems of the subjects were observed or reported during the study.

On the basis of age, peak $\dot{V}O_2$, and strength, the men were divided into three groups: no-exercise training control (NOE, $n = 5$), isotonic (model 486 T, Quinton Imaging/Ergometer, Seattle, WA) exercise training (ITE, $n = 7$), and isokinetic (Lido isokinetic ergometer, Loredan Biomedical, Davis, CA) exercise training (IKE, $n = 7$). The isokinetic exercise program was designed to maintain leg strength, and the isotonic program aerobic capacity during BR (10–13). These types of exercise programs have been employed during spaceflight to sustain fitness. After a 3-mo familiarization period, 12 subjects (4 NOE, 4 ITE, and 4 IKE) entered the Human Research Facility at Ames Research Center for testing. Eight weeks later, the other seven men (1 NOE, 3 ITE, and 3 IKE) were tested. The protocol was 7 days of ambulatory control with dietary equilibration and collection of control data, 30 days of 6° head-down BR, and then 4.5 days of ambulatory recovery. Sitting ergometer exercise (50% peak $\dot{V}O_2$) was performed for 30 min/day during ambulatory control to retard any effects of semiconfinement deconditioning. The subjects were supervised 24 h/day while in the Human Research Facility, and room lighting was on between 0700 and 2300. We have no evidence that any subject stood up during the BR period; all testing, showering, and excretory functions were done in horizontal or head-down positions. The subjects were allowed one pillow and to rise on one elbow to eat.

Diet. The diet was composed of fresh and frozen foods. Seventeen different daily menus were rotated sequentially during each 42-day study. The prescribed daily intake was 2,800 kcal for the NOE group and 3,100 kcal for the ITE and IKE groups. No caloric adjustment was made for body weight. Because of the problem with arranging meals around the exercise periods, dislike of some foods, and occasional gastrointestinal disturbances, all prescribed food was not consumed but measured. Water and other noncaloric beverages were consumed ad libitum and measured. Body weight was measured daily (horizontally during BR) in the morning after breakfast. Caloric and liquid intakes were designed to maintain body mass unchanged throughout the study.

Exercise regimens. The two exercise groups worked for two 30-min periods/day for 5 days/wk. A detailed description of the exercise protocols is provided elsewhere (10). Briefly, the ITE regimen involved continuous 2-min work bouts at 40% of peak $\dot{V}O_2$, alternating with 2-min work bout at levels of $\dot{V}O_2$ that increased progressively to 90% of peak $\dot{V}O_2$ (e.g., 2 min at 40%, 2 min at 60%, 2 min at 40%, 2 min at 70%, etc.). The IKE regimen employed 10 sets of 5 repetitions each of maximal knee flexion and extension force (90–100° range of motion) at a speed of 100°/s, taking 10 s per set followed by 50 s of rest, for a total time of 15 min. Then the other leg was exercised similarly for 15 min. All exercise training and testing were performed with the subjects in the supine position. The exercise regimens were designed to maintain peak $\dot{V}O_2$ (ITE) and muscular strength and endurance (leg work during extension and flexion) (IKE) at pre-BR levels after 30 days of BR. These measurements were used as indexes of the efficacy of the exercise training countermeasures (10–13).

Blood analyses. Blood samples were obtained in the morning (0900–1100) on *day − 3* (control) and *days 4* and *27* of BR from each subject just before the first exercise bout of the day. Blood draws occurred at the same time of day for each subject throughout the study. Samples were taken from an indwelling catheter placed 30 min earlier. Blood was placed into multiple sample tubes, inserted into ice water, and centrifuged at 4°C; individual serum and plasma aliquots for each assay were stored at −80°C until analysis. The collection of individual aliquots negated freezing, thawing, and refreezing of samples. All assays were performed within 90 days of the completion of the study. For a subject, all samples for a parameter were run within the same assays to eliminate between-assay variability. In addition, an equal number of subjects from each group were run together within an assay. Serum enzymes, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) were measured using a Cobas automated clinical analyzer (Roche Analytical Instruments, Belleville, NJ). Plasma lactate concentrations were measured by enzymatic assay (Sigma Chemical, St. Louis, MO). Plasma hormone levels were measured in duplicate by using RIA kits obtained from Diagnostic Products (Los Angeles, CA). The respective intra- and interassay coefficients of variability were 3 and 11% for cortisol, 3 and 9% for aldosterone, and 8 and 10% for progesterone, respectively. The respective intra- and interassay coefficients of variability for total testosterone were 5 and 6% and 6 and 10%, respectively, for free testosterone. Plasma norepinephrine and epinephrine were measured by electrochemical detection following extraction and separation by HPLC. The within-assay variability was 5 and 3% for norepinephrine and epinephrine, respectively, and the sensitivity was 5 pg/ml for both.

Statistical analyses. Differences within and between groups were determined by using one-way or two-way analysis of variance followed by a Newman-Keuls test. The initial value, obtained before exposure to treatment, for the various hormones was treated as a confounding variable. Differences between groups for parametric data were analyzed by one-way analysis of variance or paired *t*-test, where appropriate. Significance was determined at $P < 0.05$, and values in the text are means ± SE.

RESULTS

There were no significant changes in body mass within each group (NOE: 74.6 ± 5.3 to 73.6 ± 5.1 kg; IKE: 74.3 ± 2.4 to 73.5 ± 2.3 kg; and ITE 80.2 ± 1.5 to 80.2 ± 1.3 kg, for pre-BR and post-BR, respectively). Only one subject did not complete all of the prescribed exercise bouts; he missed 1 day of exercise due to muscle pain. The prescribed exercise regimes were effective in attenuating the negative aspects of BR (Table 1). The NOE regimen resulted in significant reduction in aerobic and muscular work capacity over the course of BR. Peak $\dot{V}O_2$ was reduced with IKE, but legwork was improved significantly, and the ITE group sustained both aerobic and muscular work capacity (10–13).

Hormone levels. After BR, and regardless of exercise group, there were no significant changes in plasma concentrations of cortisol, aldosterone, progesterone, or epinephrine (Table 2). There was, however, a significant decrease in plasma norepinephrine in the IKE group compared with the NOE group after 4 days of BR that persisted throughout BR (Table 2). Total and free testosterone levels decreased significantly in exercise groups compared with NOE, as well as within the IKE and ITE

Table 1. *Measures of countermeasure efficacy in men with no exercise, isokinetic exercise, or isotonic exercise before and during bed rest*

	Group	Pre-Bed Rest	Bed Rest *Day 27*
Peak O_2 uptake, $ml \cdot min^{-1} \cdot kg^{-1}$	NOE	44±4.1	36±3.6*
	IKE	43±3.6	40±2.2*
	ITE	39±3.6	40±2.9
Leg total work			
Flexion, N·m	NOE	489±44.6	396±46.8*
	IKE	410±29.9	435±48.7
	ITE	432±40.0	375±25.4
Extension, N·m	NOE	939±89.2	776±90.0*
	IKE	789±59.4	1000±77.9*
	ITE	837±56.9	796±55.3

Values are means ± SE. NOE, no-exercise group ($n = 5$); IKE, isokinetic exercise group ($n = 7$); ITE, isotonic exercise group ($n = 7$). *$P < 0.05$ from pre-bed rest.

Table 2. *Plasma hormone levels in men with no exercise, isokinetic exercise, or isotonic exercise before and during bed rest*

	Group	Pre-Bed Rest	Bed Rest *Day 4*	Bed Rest *Day 27*
Cortisol, μg/dl	NOE	16.7±3.66	15.6±2.38	16.5±1.25
	IKE	13.2±1.41	11.7±0.99	13.1±1.07
	ITE	15.0±3.12	15.4±2.38	14.9±2.36
Aldosterone, ng/dl	NOE	12.7±1.81	12.3±1.29	10.2±1.21
	IKE	9.6±.79	8.5±1.39	8.7±1.54
	ITE	13.5±1.93	8.8±0.88	9.4±0.88
Progesterone, ng/ml	NOE	0.43±0.06	0.37±0.07	0.32±0.08
	IKE	0.37±0.04	0.35±0.06	0.34±0.07
	ITE	0.34±0.05	0.30±0.03	0.33±0.04
Norepinephrine, pg/ml	NOE	150±31.0	192±37.1	141±33.6
	IKE	142±28.9	105±6.6*	102±15.8*
	ITE	145±20.5	134±16.5	107±36.9
Epinephrine, pg/ml	NOE	27±4.3	12±1.8	26±11.6
	IKE	37±11.9	21±5.1	20±3.0
	ITE	30±6.5	18±3.5	38±13.4

Values are means ± SE. NOE, $n = 5$; IKE, $n = 7$; ITE, $n = 7$. *$P < 0.05$ from pre-bed rest.

Table 3. *Indexes of overtraining syndrome*

	Group	Pre-Bed Rest	Bed Rest *Day 4*	Bed Rest *Day 27*
LDH, IU/l	NOE	123±9.5	102.5±10.6*	94±9.7*
	IKE	141±11.2	115.33±8.3*	119±10.0*
	ITE	125±13.3	153±20.7	171±29.0*
CPK, IU/l	NOE	137±21.2	97±23.4	95±28.0*
	IKE	172±17.6	151±15.9	117±10.4*
	ITE	130±11.4	117±13.2	83±8.14*
Lactate, mg/dl	NOE	8.5±1.95	10.8±1.16	8.1±1.68
	IKE	8.3±1.35	8.4±1.28	8.4±1.05
	ITE	7.5±0.81	10.6±2.64	8.8±1.12
Resting heart rate, beats/min	NOE	66±4.3	67±1.5	70±6.1
	IKE	59±3.6	59±1.9	61±2.5
	ITE	67±2.0	68±3.4	65±2.3

Values are means ± SE. LDH, lactate dehydrogenase; CPK, creatine phosphokinase. *$P < 0.05$ from pre-bed rest.

groups (Fig. 1). However, the type of exercise did not appear to affect the magnitude of the reduction in testosterone levels. As both total and free testosterone levels changed proportionally in response to exercise, there was no difference in the free to total testosterone ratio over time or between groups.

Indexes of the OTS. The LDH levels decreased ($P < 0.05$) in both the NOE and IKE groups (Table 3), whereas they increased significantly in the ITE group over time. The CPK levels decreased in all groups during BR, whereas resting heart rate and plasma lactate levels were not changed significantly (Table 3).

DISCUSSION

The BR exercise loads and regimens in the present study were designed to sustain aerobic capacity or muscle strength, which was accomplished in both exercise-training groups (10–13). Although the efficacy of the exercise countermeasures designed to prevent the specific aspects of disuse was demonstrated, possible adverse effects were not addressed initially. We hypothesized that, at the required heavy workloads to maintain aerobic capacity and muscle strength, there may be alteration of plasma steroid concentrations due possibly to OTS.

Indexes of the OTS are ill-defined (8, 34). Inability to complete subsequent work bouts, due to fatigue or injury, is a classic indication of OTS. In the present study, all but one of the subjects completed the exercise protocols (he missed only 1 day of exercise). Whereas the intensity and duration of the exercise regimens were designed for maximal effort to maintain aerobic fitness or muscle strength, they were not debilitating, nor did they limit performance. An increase in resting heart rate is postulated to be indicative of the OTS; however, no such change was noted in the present subjects, nor did we find a significant difference between groups in resting plasma

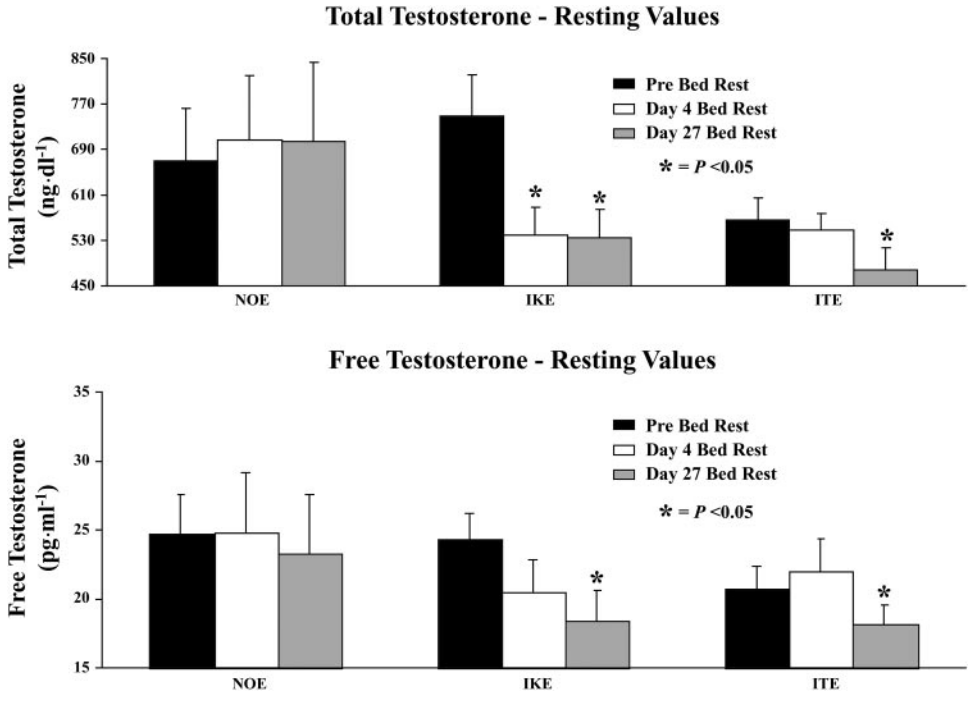

Fig. 1. Plasma total and free testosterone of men with no exercise (NOE, $n = 5$), isokinetic exercise (IKE, $n = 7$), or isotonic exercise (ITE, $n = 7$) before and during bed rest. Values are mean ± SE. *$P < 0.05$ from pre-bed rest.

lactate concentrations, another proposed marker of the OTS. Elevation of serum enzyme levels is also suggested as a sign of the OTS. During BR, there was a significant decrease in CPK in all groups. Although LDH did not change in the NOE or IKE groups, it increased significantly in the ITE group, which could be indicative of an overtraining effect. A rise in LDH results from heavy physical exertion (5, 8), but it is usually accompanied by an increase in CPK, which was not observed in this study. Thus there was no overwhelming enzyme or hormonal evidence of overtraining in the exercise groups during BR. However, earlier data by DeRoshia and Greenleaf (4) noted alterations in mental performance and mood-state parameters in the ITE group that the authors attributed to chronic exercise-induced overfatigue.

In previous studies of high-intensity exercise in ambulatory subjects, we and others have reported a reduction in plasma free and total testosterone in men (6, 8, 24, 34). However, these reductions were associated with clear indexes of the OTS: an increase in resting heart rate, an elevation of plasma enzymes (i.e., LDH, CPK), and a decrease in exercise performance (6, 8, 24, 34, 36, 37). In the absence of these OTS changes, there was no alteration in testosterone concentrations (39). In the presence of OTS indexes, there were significant alterations in concentrations of other steroids, indicative of changes in steroidogenesis. In the present study, the observed testosterone reductions during BR in the exercise groups do not appear to be related to OTS but to other factors associated with these exercise regimens.

BR plasma steroid concentrations. In the present study, there were no changes in the concentrations of the steroids (free and total testosterone, cortisol, aldosterone, or progesterone) measured in the NOE group. Thus there did not appear to be an effect of BR alone on plasma steroid concentrations. As with spaceflight, the responses of hormones to BR have been highly variable. This may be due to differences in procedures, interactions between the subjects and staff, limited numbers of subjects, and the countermeasures investigated. However, significant changes in each of the steroids of interest have been reported. Vernikos et al. (35) found that male subjects exhibited an increase in cortisol with a reduction in aldosterone during 7 days of BR, whereas female subjects had a decrease in plasma cortisol and an increase in aldosterone concentrations. Furthermore, the men had no change in testosterone concentrations, and the women had no change in progesterone or estrogen over the course of the study. In a comparison of men and women during 7 days of BR, Blanc et al. (2) failed to note differences in plasma cortisol concentrations in either gender. In a 42-day BR study, plasma cortisol increased over the first 4 wk but returned to control levels thereafter (1). The same investigators found plasma aldosterone increased during studies of a similar duration (18–21), whereas others reported that plasma cortisol, total testosterone, and free testosterone were not altered (7). In male subjects exposed to BR for 120 days, there was a slight (nonsignificant) reduction in testosterone (22). In these disparate studies, an influencing factor may be the initial level of physical conditioning of the subjects. Zorbas et al. (40) contrasted the response of trained and untrained subjects to 30 days of BR. In response to BR, untrained subjects had no significant changes in plasma concentrations of cortisol, aldosterone, or testosterone, whereas, in the trained subjects, there were reductions in all steroids. Overall, these data point to probable changes in plasma steroid concentrations during BR, which may be related to the initial fitness level of the subject. However, in the present study, the absence of change in the primary end products of steroidogenesis pathways (testosterone, cortisol, and aldosterone) does not support an alteration during BR alone.

Countermeasure impact. A variety of countermeasures are used to attenuate the various adverse effects of BR and spaceflight. These countermeasures include the following: *1*) performance of aerobic exercise to maintain work capacity; *2*) performance of resistance exercise to maintain muscle mass and strength; *3*) activation of body negative pressure to attenuate the orthostatic intolerance after BR; and *4*) a pharmacopoeia of pharmacological interventions. There are few investigators who addressed the possible influence of these countermeasures on plasma steroid concentrations. Gharib et al. (9) assessed the efficacy of lower body negative pressure (LBNP) to negate the orthostatic intolerance that occurred after BR of 30 days. Over the course of the study, there was an increase in plasma aldosterone in the control subjects but no difference in the LBNP group. Maillet et al. (19) employed a combination of exercise and LBNP during a 30-day BR study and found an increase in plasma aldosterone in both test groups but a greater increase in the control group. In a subsequent study of women during 120 days of BR, which employed multiple countermeasures, both plasma cortisol and aldosterone were increased to a greater extent in subjects not undertaking countermeasures (20). Plasma testosterone was reduced more in control subjects than in those employing countermeasures in a similar 120-day BR experiment (22). These data, while inconsistent, suggest that use of exercise countermeasures can alter plasma steroid concentrations during BR. The finding of significant changes in free and total plasma testosterone with exercise countermeasures in the present study supports this. However, we observed no change in other plasma steroids, which may have been due to our dietary control and subsequent maintenance of body mass.

There was no effect of BR deconditioning on plasma testosterone concentrations in the present study, but there were reductions in both free and total testosterone, regardless of the type of exercise regimen, during BR. The free-to-total testosterone ratio did not change in any group, indicating no change in the sex hormone-binding globulin concentrations. The role and amount of sex hormone-binding globulin, as well as other testosterone-binding proteins, do not change with intensity-dependent exercise training in ambulatory subjects (22, 34). Therefore, the changes in free testosterone in the present study, in response to exercise training during BR, are due most likely to alterations in synthesis or metabolism rather than to the concentration of binding proteins.

Summary. The present observations of a reduction in plasma testosterone associated with both IKE and ITE training regimens during BR support our hypothesis that exercise countermeasures may contribute to changes in plasma steroid concentrations during spaceflight. However, the effect of exercise-intensive countermeasures on plasma testosterone is not directly associated with indexes of overtraining. The reduction in plasma concentrations of testosterone with heavy exercise during spaceflight could be a contributing factor to the loss of muscle and bone mass observed in astronauts. Thus the volume and intensity of the exercise should be titrated to avoid a

reduction of plasma testosterone and thus compromising the effectiveness of the countermeasure in sustaining muscle strength and aerobic capacity.

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